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Autoimmune conditions and comorbid depression in pregnancy: examining the risk of preterm birth and preeclampsia

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Abstract

Objective—Determine whether prenatal depression interacts with autoimmune conditions to further increase the risk of preterm birth or preeclampsia.

Study design—Our sample included 3,034 pregnant women with rheumatoid arthritis (RA), Crohn's disease (CD), psoriasis, or controls that were prospectively enrolled into MothertoBaby pregnancy studies. We estimated the independent and joint effects of the three autoimmune conditions and depression on the select outcomes.

Results—We found an increased risk of preterm birth among women with RA (2.10, 95% CI 1.54, 2.87), CD (1.87, 95% CI 1.25, 2.81) or psoriasis (1.88, 95% CI 1.27, 2.79) independent of depression status. RA was also independently associated with preeclampsia. Prenatal depression was not independently associated with preterm birth or preeclampsia, nor was there any synergism with autoimmune conditions.

Conclusions—If these findings are confirmed, the absence of synergism should be encouraging news to the many women with select autoimmune conditions and depression in pregnancy.

Introduction

Autoimmune conditions are more prevalent in women than men, and often occur during a woman's reproductive years.[1] Generally, autoimmune conditions are not thought to substantially affect fertility,[2] and thus many women and their clinicians are confronted with concerns about how autoimmune disease may affect pregnancy and birth outcomes. Autoimmune conditions have been associated with adverse birth outcomes, including preterm birth and preeclampsia;[1] disease activity may increase these risks.[3,4]

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Depression, like many autoimmune conditions, is more prevalent in women and affects many during their reproductive years. According to the Centers for Disease Control, in the United States between 2009–2012, an estimated 9.3% of women ages 18–39 had moderate or severe depressive symptoms.[5] Depression in pregnancy has also been associated with similar adverse birth outcomes as autoimmune conditions, including preterm birth and preeclampsia,[6,7] although the findings are contradictory, and some have suggested that these associations result from medications taken for depression in pregnancy.[8,9]

As a result of the overlapping distributions of depression and autoimmune conditions in young women of reproductive age, it is not unexpected that they co-occur. Depression is a reported comorbidity of many autoimmune conditions,[10–13] and has been associated with reduced quality of life[11,14,15] in individuals with autoimmune disease. For example, patients with rheumatoid arthritis and comorbid depression have disproportionally worse functioning, decreased response to treatment, higher pain and increased disease activity.[11] Proposed mechanisms of the two exposures have been bidirectional, with depression affecting disease activity and vice versa through biological, psychological, and behavioral pathways.[15]

There is a dearth of literature examining these comorbidities in a pregnant population. Our group has reported that a disproportionate prevalence of comorbid depression and psoriasis persists in pregnancy;[16] however, to our knowledge, there are no published reports on the effects of prenatal depression on birth outcomes in the offspring of women with autoimmune conditions. Given the commonalities in adverse birth outcomes from both autoimmune conditions and prenatal depression and the comorbidity of the exposures, it is critical that we investigate the potential synergism of these exposures on pregnancy and birth outcomes. Using a sample from a prospective cohort of women enrolled into MotherToBaby pregnancy studies, we hypothesized that: 1) women with rheumatoid arthritis (RA), Crohn's disease (CD) and psoriasis have an increased risk of preeclampsia and preterm birth relative to controls; 2) prenatal depression independently predicts preeclampsia and preterm birth; 3) synergism results between the two exposures on the risk of preterm birth and preeclampsia.

Materials and Methods

Study sample

Subjects included in this analysis are a sample of 3,034 women enrolled into the MotherToBaby pregnancy studies between 2009–2015 that had a live birth. MotherToBaby, a service of the Organization of Teratology Information Specialists, provides evidence-based information about the risks of medications, chemicals, herbal products, illicit drugs, and diseases in pregnancy. MotherToBaby conducts prospective pregnancy studies to assess a spectrum of adverse pregnancy and birth outcomes in pregnancies exposed to diseases or therapeutic agents (including autoimmune diseases) relative to unexposed pregnancies. Details of study design and subject recruitment have been previously described.[17] Briefly, subjects residing in the United States or Canada that speak English or Spanish are recruited through three primary mechanisms: 1) invitation to participate after calling the toll-free MotherToBaby telephone service; 2) direct-to-healthcare provider promotion for specific diseases, or 3) direct-to-consumer recruitment through the Internet/social media.

MotherToBaby pregnancy studies were approved by the University of California, San Diego Institutional Review Board.

Study design and data collection

Upon enrollment in pregnancy, women are interviewed by telephone up to three times (any time before 20 weeks of gestation, 20–22 weeks of gestation, and 32–34 weeks of gestation, depending upon gestational age at enrollment). Women are queried about their family medical history, prescription and non-prescription medication exposures during pregnancy, tobacco use, previous pregnancy outcomes, and socioeconomic and demographic characteristics of the woman and her partner. The exposure history includes start and stop dates, dosage changes and frequencies for all medications, herbal supplements, vitamins, occupational exposures, and prenatal care testing or other procedures. Medical records are requested from OBGYNs and any specialty providers that managed the woman's care in pregnancy. Self-reported exposures and diagnoses are confirmed by medical records when possible; discrepancies prompt further query of the woman.

Birth outcomes are obtained using a standard questionnaire conducted by telephone shortly after delivery. Women update exposure information, and report on birth outcomes, including live birth, stillbirth, elective termination, or spontaneous abortion, the presence or absence of major structural defects, gestational age at delivery, mode of delivery, infant Apgar scores, and infant birth weight, length, and head circumference. Additionally, medical records from the delivery hospital and pediatrician are requested for data abstraction and verification.

Exposures and outcomes

Subjects for this analysis were selected from the entire MotherToBaby database based upon self-report of one of the following: 1) RA; 2) CD; 3) psoriasis; or 4) no history of any of the following autoimmune diseases: RA, CD, psoriasis, psoriatic arthritis, lupus, ankylosing spondylitis, other autoimmune disease, antiphospholipid syndrome, celiac disease, connective tissue disease (mixed/undifferentiated), fibromyalgia, or ulcerative colitis (controls).

Depression was defined as a self-report of a diagnosis of depression that was not reported to be resolved, situational, or postpartum depression from a previous birth. Additionally, medications reported as taken by the mother in pregnancy and indicated for depression were categorized into trimester of use.

Preterm birth was defined as delivery prior to 37 weeks of gestation. Gestational age at delivery was based upon the self-reported last menstrual period of the mother and confirmed by medical records when possible. Discrepancies are resolved by ultrasound dating whenever possible. Preeclampsia was self-reported and verified with medical records when possible.

Statistical analysis

Frequencies and means were used to summarize all variables. Hypothesized causal models were created to identify confounders and potential selection biases for multivariable

adjustment.[18] We adjusted for race/ethnicity, socioeconomic status (measured using Hollingshead score[19] based on occupation and education of the mother and her partner; dichotomized into high (>29) versus low (≤29)), medical comorbidities (high blood pressure, thyroid disorder and type-1 diabetes), pregnancy smoking, pre-pregnancy body mass index (BMI), maternal age at estimated due date, and gestational age at enrollment. To create propensity scores, we regressed each autoimmune condition on the potential confounders and outputted the probabilities to create propensity scores for adjustment. The computed probability of exposure (i.e.- probability of each autoimmune condition) was then included in the regression models as a continuous variable. The covariate for depression in pregnancy was omitted from propensity scores to estimate its independent effects with preterm birth and preeclampsia. Depression medication use was initially categorized into each of the three trimesters, but due to thin strata was collapsed into any antidepressant medication use during pregnancy.

Risk ratios for preterm birth were then estimated using logistic regression with a log link and a Poisson distribution. Models were first created with main effects of the autoimmune condition (RA, CD or psoriasis in separate models), depression and depression medications. However, due to the small sample of women taking depression medications, the covariate was dropped from models. Effects on the point estimates for autoimmune conditions and depression were minimal (<5%). Interaction terms for the autoimmune condition and depression were then included in each model to assess multiplicative joint effects. Separate models were constructed for RA, CD and psoriasis, and models were adjusted with propensity scores. Propensity score adjusted linear regression models were also created to estimate the average difference in the number of weeks of gestation associated with the autoimmune conditions. All analyses were then repeated to estimate the risk of preeclampsia. To assess additive interaction between autoimmune conditions and depression, we tested the relative excess risk due to interaction (RERI). By creating indicator variables for combinations of the autoimmune condition (yes/no) and depression (yes/no), parameter estimates and a covariance matrix were entered into a calculator (available at http://www.epinet.se) assessing additive interactions.[20] Finally, to assess effect measure modification by prenatal depression, logistic regression models for preterm birth and preeclampsia were stratified by prenatal depression status.

In sensitivity analyses, we excluded late enrollees (gestational age at enrollment >20 weeks). The data analysis for this paper was generated using SAS software, version 9.4 (Cary, NC, USA).

Results

In our final sample, 3,034 women had a singleton live birth. Of these, 1,703 had no diagnosis of an autoimmune disease as defined in the methods. For those with a single autoimmune diagnosis, 93% of those with RA, 72% with CD and 46% with psoriasis reported taking a medication for their autoimmune condition at some point during pregnancy.

We found slightly elevated prevalence of self-reported depression in women with RA (11.0%) or CD (11.3%) compared to control subjects (8.9%). Women with psoriasis had twice the prevalence of depression (18.9%) compared to controls ($p<0.0001$).

Participants were majority non-Hispanic White, and approximately 50% were nulliparous at enrollment. Women with RA, CD or psoriasis were more likely to have a preterm birth. Women with psoriasis were more likely to report having depression than the other groups, although their frequency of depression medication use did not differ. Additionally, women with psoriasis tended to have higher pre-pregnancy BMI, report gestational diabetes in pregnancy, and smoke in pregnancy compared with the other three groups. Women with RA were more likely to report other medical comorbidities (high blood pressure, thyroid disorder or Type 1 diabetes), and they were less likely than the other groups to report additional psychiatric conditions (e.g. anxiety, schizophrenia) (Table 1).

Preterm birth

Women with RA, CD or psoriasis had increased risk of preterm birth compared to women with no autoimmune conditions (Table 2). In linear regression models, women with RA delivered on average 0.55 weeks earlier (95% CI −0.74, −0.36) compared to women without RA. Women with Crohn's disease had average gestations reduced by 0.61 weeks (95% CI −0.85, −0.36) and women with psoriasis had gestations reduced by 0.30 weeks (95% CI −0.55, −0.05) compared to women without these autoimmune conditions (data not shown). Prenatal depression was not an independent risk factor for preterm birth in any of the models. There was no additive or multiplicative interaction between the autoimmune disease and depression in any models ($p>0.10$ in all models). There was indication of effect measure modification by prenatal depression on the effect estimate of psoriasis; women with prenatal depression had a stronger risk of preterm birth from psoriasis than women without prenatal depression, although confidence intervals overlapped.

Preeclampsia

When examining the risk of preeclampsia (Table 3), only RA was independently associated with preeclampsia. The effect estimates for CD and psoriasis were elevated but did not reach statistical significance. Again, there was no additive or multiplicative interaction between the autoimmune disease and depression in any models ($p>0.10$ in all models). There was also no evidence of effect measure modification by prenatal depression.

Sensitivity analyses

In sensitivity analyses restricted to the sample of women who enrolled prior to 20 weeks of gestational age, results did not change (data not shown).

Discussion

Our findings of an increased risk of preterm birth and preeclampsia from RA are similar to those of others. In a large population based cohort study of 1.9 million births in Denmark, offspring born to mothers with RA were almost 50% more likely to be born prematurely (RR 1.48, 95%CI 1.20, 1.84).[21] Reed et al. reported a slightly higher risk of preterm birth

(RR 1.78, 95% CI 1.21, 2.60) in an analysis of birth records from Washington State between 1987–2001.[22] The same authors estimated a 55% increased risk of preeclampsia from RA (RR 1.55, 95% CI 0.97, 2.50), which was very similar to our findings. The increased risk of both outcomes in women with RA suggests that preeclampsia may be a mediator in the risk of preterm birth; future work may consider formal mediation analyses.

Our findings of an elevated risk of preterm birth from CD are also similar to previous studies. Using a cohort from the Swedish health registers including 470,110 singleton births, Broms et al. reported women with CD had higher odds of preterm birth than control women (OR, 1.65; 95% CI, 1.33–2.06).[3] An earlier paper using medical birth registries in Sweden and Denmark found increased risk of moderately and very preterm birth (prevalence odds ratio [POR], 1.76; 95% CI, 1.51–2.05; and POR, 1.86; 95% CI, 1.38–2.52, respectively) from CD, but no increase in the risk of preeclampsia.[23] Our effect estimates for CD and the risk of preeclampsia in the full sample were not statistically significant, although they were elevated and only slightly crossed the null. Additionally, in the stratum of women without depression, effect estimates were statistically significant (1.82, 95% CI 1.01, 3.30).

Finally, the evidence with regards to psoriasis and our select pregnancy outcomes is more limited and conflicting.[24] Similar to our findings, Lima et al. found an increased odds for preterm birth/low birth weight composite (OR 2.02, 95% CI 1.19, 3.76) in women with psoriasis, but not for preeclampsia. However, an analysis of nationwide medical records from births in Taiwan found no increased risk for either outcome with psoriasis.[25] Our effect estimate for the risk of preeclampsia from psoriasis was not statistically significant, although it was elevated and may lack power from the relatively small sample size. Similar to our findings with Crohn's disease, our findings suggest that these autoimmune conditions may modestly increase the risk of preeclampsia, and should be considered in the care of pregnant women.

Overall, our risk estimates of preterm birth, while similar to previous estimates, were slightly stronger. This may be due to the selection of our sample compared with previous research. These select autoimmune conditions are generally rare, leading many to conduct research from population medical registries for sufficient sample size. In contrast, our cohort was comprised of women who, as a result of their disease, chose to participate in the study. This self-selection may result in a sample with higher disease severity and stronger risks for adverse pregnancy outcomes than large scale, record-based analyses.

When discussing our results, the limitations of our analyses should be considered. Non-diseased women who volunteered for our studies may be healthier than the general population, as noted by the small proportions of control subjects who smoked in pregnancy or did not report prenatal vitamin use. With respect to our exposure and outcomes, the prevalence of depression (8.9%) and preeclampsia in our controls (3.5%) was similar to the United States (US) prevalence (9.3% in 2009–12, and 3.8% in 2010, respectively).[5,26] However, the prevalence of preterm births (5.9%) was much lower than that of the US (11.5% in 2012).[27] This may have biased our autoimmune disease effect estimates for preterm birth away from the null. Also, although outside of the scope of this analysis, we did not address medication use for the autoimmune conditions or disease severity with the

outcomes, which may contribute to the risk estimates. Additionally, our sample of those with comorbid autoimmune conditions and depression was small, limiting our power to detect joint effects. Further, prenatal depression was self-reported with no measure of severity, although we would expect misclassification to be non-differential, potentially attenuating effect estimates. However, adding confidence to our estimates, 49% of women in our sample with self-reported depression were on an antidepressant medication during pregnancy, consistent with use in a general pregnant population.[28] Finally, the indication of preterm birth (medically indicated, preterm premature rupture of the membranes, or spontaneous preterm birth) was not available at the time of data analysis. Investigation into whether the indication varied by autoimmune condition and its contribution to the observed increased risk is of preterm birth and should be considered in future research.

To our knowledge, this was the first study to assess the independent and joint effects of both autoimmune disease and depression on pregnancy outcomes. There is biologic rationale for our hypothesis of joint effects. It is hypothesized that systemic inflammation from the autoimmune condition contributes to the high level of depression, as depression itself is associated with an increase in inflammatory cytokines and acute-phase reactants.[29] Birth outcomes such as preeclampsia[30] and preterm birth[31] have also been associated with inflammatory cytokines, leading us to hypothesize that women with both exposures have an even greater risk of these outcomes. Ultimately our data did not support this hypothesis, as maternal self-reported prenatal depression was not a risk factor for either preterm birth or preeclampsia in women with select autoimmune diagnoses. We did find potential effect measure modification by depression in the effects of psoriasis on preterm birth, as women with depression had a stronger risk of preterm birth from psoriasis than women without depression. However, confidence intervals were wide and overlapping, warranting further investigation. Maternal depression in this sample was not confirmed or classified by administration of symptom severity rating scales, likely resulting in a heterogeneous categorization of depression. Medications for depression, less likely to be as heterogeneous, had stronger effect estimates but very wide confidence intervals due to the small sample of exposed with the selected outcomes and were ultimately removed from models. Another interpretation of these results is that the strength of the associations of our select autoimmune conditions with preterm birth and preeclampsia make any comparison of risk from depression minimal. In a review of 47 studies of prenatal depression and preterm birth conducted since 1984, only 12 found statistically significant associations between depression and preterm birth, and effect measure ratios ranged from 1.3–4.9.[7] Similarly, in analysis of pregnant women with untreated depression, antidepressant treated depression, or no depression, only those that took antidepressants in pregnancy had an increased risk of preeclampsia.[8] Thus, while depression may operate on preterm birth and preeclampsia through similar inflammatory pathways as autoimmune diseases, the effects are likely weaker than those of RA, CD and psoriasis, and may not be measurably adding to the risk in these women.

This study adds to the literature by estimating the risks of preterm birth and preeclampsia from RA, CD and psoriasis. Further, we have expanded the study of autoimmune conditions in pregnancy by evaluating whether prenatal depression confers additional risk for preterm

birth or preeclampsia in women with our selected autoimmune conditions, which up until this point had not been reported.

In summary, women with RA, CD or psoriasis were more likely to have a preterm birth than control women. Self-reported depression in pregnancy was not associated with either of these outcomes. While our lack of independent or joint effects of prenatal depression may be welcome news to clinicians and women managing both exposures in pregnancy, subsequent studies should be performed utilizing larger datasets with more detailed depression information. Further research will complement our findings as we evaluate the important question of whether prenatal depression is indeed a modifiable risk factor for adverse pregnancy outcomes in women with select autoimmune conditions.

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Table 1

Pregnancy and sociodemographic characteristics of women enrolling in MotherToBaby pregnancy studies by autoimmune condition (n=3,034[a]).

	Rheumatoid Arthritis n=729	Crohn's Disease n=348	Psoriasis n=330	Control n=1703
Pregnancy and birth outcomes	n (%)	n (%)	n (%)	n (%)
Preterm birth (<37 weeks)	105 (14.4)	40 (11.5)	47 (14.2)	100 (5.9)
Preeclampsia	42 (5.8)	18 (5.2)	21 (6.4)	60 (3.5)
Maternal depression	80 (11.0)	41 (11.3)	58 (18.9)	153 (8.9)
Depression medications in pregnancy	40 (50.0)	11 (26.8)	30 (51.7)	83 (54.2)
Medical comorbidities[b]	117 (16.1)	22 (7.3)	36 (10.9)	175 (10.3)
Other psychiatric condition	45 (6.2)	32 (9.2)	39 (11.8)	188 (11.0)
Gestational diabetes	58 (7.9)	24 (6.9)	33 (10.0)	91 (5.3)
Other maternal factors				
Maternal age (mean, sd)	32.5 (4.8)	31.5 (4.4)	32.6 (4.8)	32.1 (5.1)
Gestational age at enrollment (mean, sd)	14.4 (7.7)	15.7 (8.8)	16.2 (8.4)	22.0 (9.2)
Gestational age at delivery (mean, sd)	38.6 (2.1)	38.6 (2.3)	38.7 (2.3)	39.3 (1.9)
Pre-pregnancy BMI (mean, sd)	25.0 (5.9)	24.6 (4.9)	26.9 (6.7)	24.7 (5.5)
Infant birth weight (kg) (mean, sd)	3.2 (0.6)	3.3 (0.6)	3.3 (0.6)	3.4 (0.5)
Socioeconomic status (low)	58 (8.0)	21 (6.0)	29 (9.0)	188 (11.0)
Nulliparity	348 (47.7)	206 (59.2)	169 (51.2)	877 (51.5)
Race/ethnicity				
non-Hispanic White	565 (77.5)	319 (91.7)	275 (83.3)	1240 (72.8)
Hispanic	91 (12.5)	8 (2.3)	20 (6.1)	263 (15.4)
African American	22 (3.0)	15 (4.3)	15 (4.6)	81 (4.8)
Asian/other	51 (7.0)	6 (1.7)	20 (6.1)	119 (7.0)
Maternal pregnancy smoking	49 (6.7)	35 (10.1)	46 (18.1)	69 (4.1)
No prenatal or multivitamin use	1 (0.1)	1 (0.3)	1 (0.3)	5 (0.3)

[a] 13 individuals with Crohn's disease also have RA; 21 have psoriasis and RA; 36 have psoriasis and Crohn's disease; 3 have all 3 conditions.

[b] includes high blood pressure, thyroid disorder and Type 1 diabetes.

Table 2

Independent effects (adjusted risk ratios[a]) of autoimmune conditions and depression on preterm birth.

	Number of subjects		Number of preterm births			Risk ratio stratified by depression status	
	Exposed[b]	Unexposed[b]	Exposed[b]	Unexposed[b]	Adjusted[a] risk ratio (aRR)	Adjusted[a] risk ratio (aRR) in women without depression	Adjusted[a] risk ratio (aRR) in women with depression
					n=2373[c]	n=2149	n=224
Rheumatoid Arthritis	729	1703	105	100	2.10 (1.54, 2.87)	2.12 (1.54, 2.93)	2.09 (0.71, 6.16)
Depression					1.01 (0.63, 1.60)		
					n=1995	n=1809	n=186
Crohn's disease	348	1703	40	100	1.87 (1.25, 2.81)	1.82 (1.18, 2.80)	2.89 (0.80, 10.44)
Depression					1.16 (0.68, 1.98)		
					n=1980	n=1777	n=203
Psoriasis	330	1703	47	100	1.88 (1.27, 2.79)	1.74 (1.13, 2.70)	2.79 (1.11, 7.00)
Depression					1.40 (0.89, 2.21)		

[a] Propsensity scores for adjustment include race/ethnicity, socioeconomic status, medical comorbidities, pregnancy smoking, pre-pregnancy BMI, and maternal age, and gestational age at enrollment.

[b] Number of subjects exposed and unexposed to select autoimmune condition.

[c] n's represent complete case analysis.

Table 3

Independent effects (adjusted risk ratios[a]) of autoimmune conditions and depression on preeclampsia.

	Number of subjects		Number of preeclampsia outcomes			Risk ratio stratified by depression status	
	Exposed[b]	Unexposed[b]	Exposed[b]	Unexposed[b]	Adjusted[a] risk ratio (aRR)	Adjusted[a] risk ratio (aRR) in women without depression	Adjusted[a] risk ratio (aRR) in women with depression
					n=2368[c]	n=2144	n=224
Rheumatoid Arthritis	726	1700	42	60	1.62 (1.04, 2.53)	1.65 (1.04, 2.63)	1.08 (0.21, 5.55)
Depression					0.94 (0.48, 1.88)		
					n=1991	n=1805	n=186
Crohn's disease	347	1700	18	60	1.67 (0.93, 3.00)	1.82 (1.01, 3.30)	NE
Depression					0.56 (0.20, 1.54)		
					n=1977	n=1744	n=203
Psoriasis	330	1700	21	60	1.57 (0.89, 2.77)	1.58 (0.86, 2.89)	1.39 (0.25, 7.61)
Depression					0.73 (0.33, 1.59)		

[a]Propsensity scores for adjustment include race/ethnicity, socioeconomic status, medical comorbidities, pregnancy smoking, pre-pregnancy BMI, and maternal age, and gestational age at enrollment.

[b]Number of subjects exposed and unexposed to select autoimmune condition.

[c]n's represent complete case analysis.

NE=no estimate. There were no cases of preeclampsia among individuals with Crohn's disease in the stratum with depression.